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Copper-Catalyzed Cascade Cyclization for the Synthesis of Trifluoromethyl-Substituted Spiro-2*H*-azirines from 1,6-Enynes

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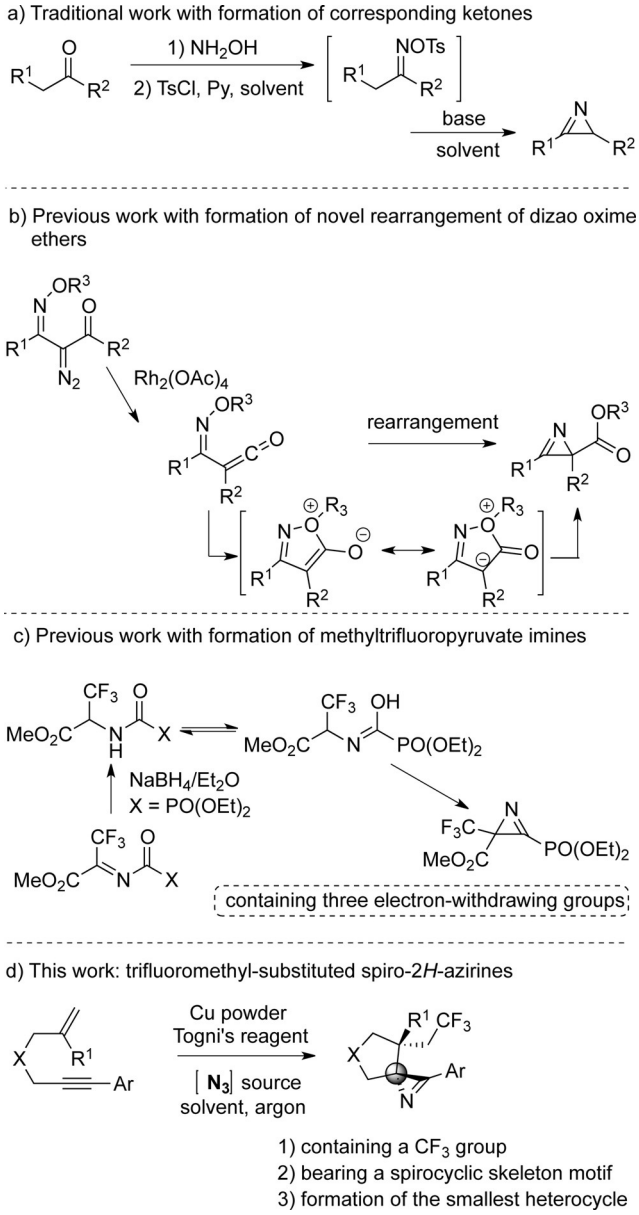
Abstract: A method for the synthesis of trifluoromethyl CF_3-substituted spirocyclic compounds containing with a unique quaternary carbon center from readily available starting materials has been developed. The reaction provides a facile access to 2*H*-azirines *via* cascade cyclization. These compounds constitute a new class of functionalized synthetic intermediates, which can be used for the synthesis of various nitrogen-containing heterocycles and biologically active CF_3-containing compounds.

Keywords: 2*H*-azirines; cascade cyclization; copper; enynes; spirocyclic skeleton

The unusual synthetic motif of the 2*H*-azirines makes them important reactive intermediates with ever-increasing applications in organic synthesis.[1] They are stable towards manipulation of the unique structure featuring a C=N bond embedded in a highly strained three-membered cycle, and they have been exploited as useful precursors for constructing different azacyclic compounds by using transition metal catalysis or UV light irradiation.[2] In addition, as unique building blocks, 2*H*-azirines have been used for the synthesis of various nitrogen-containing heterocycles, such as indoles,[3] pyrroles,[4] pyridines,[5] isoxazoles[6] and others.[7] Both the cleavage of C–N and C–C bonds were classified to be general strategies for the ring-opening reaction of 2*H*-azirines. Despite broad utility, the synthesis of this unique structure is rarely studied.[8] The traditional synthetic method relied on the use of the corresponding ketones (Scheme 1a).[9] The limited approaches to 2*H*-azirines has seriously hampered the further exploitation of their synthetic potential. Thus, the development of practical synthetic methods to construct new functionalized 2*H*-azirines is of great interest. With these demands in mind, Park and co-workers developed a method for the synthesis of quaternary carbon centered 2*H*-azirine-2-carboxylic esters by the rearrangement of α-diazo oxime ethers (Scheme 1b).[10] Although this process enables an efficient synthesis of 2*H*-azirines, the hardly accessible substrates and the use of noble-metal catalysts restrict its further application in synthetic chemistry.

Highly substituted pyrrolidines are ubiquitous substructures in a large number of natural alkaloids exhibiting important biological activities.[11] Various synthetic methods have been developed reported towards substituted pyrrolidine derivatives synthesis, such as the reaction *via* cyclization of *N*-linked 1,6-enynes.[12] However, the construction of quaternary carbon centered spirocyclic pyrrolidines is still a challenge. With recent development of radical chemistry, the cascade radical cyclization of 1,6-enynes provides a new way for the synthesis of valuable pyrrolidines.

Thus, we speculated whether both azirine and pyrrolidine could be simultaneously achieved in one process. On the other hand, the introduction of important functionalized groups, such as CF_3 group,[13–16] into building blocks is also highly desirable. In this context, we are interested in the synthesis of trifluoromethyl-substituted azirines with structural complexity, which could show great potential of subsequent transformation in organic synthesis. The synthesis of such a unique structure was previously studied by the Röschenthaler group who used imine substrates with a pre-introduced CF_3 group (Scheme 1c).[17] To the best of our knowledge, the introduction of a new CF_3 group to construct trifluoromethyl-substituted 2*H*-azirine from readily available starting materials has not been reported. Herein, we disclose a one-pot route to trifluoromethylated spiro-2*H*-azirines *via* a copper-catalyzed cascade cyclization of 1,6-enynes

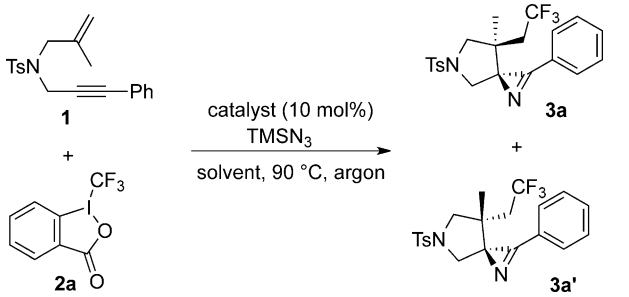


Scheme 1. Previous and proposed methodologies for the synthesis of 2*H*-azirines.

(Scheme 1d). The significance of the present reaction is three-fold: (i) The produced 2*H*-azirines represent not only a highly valuable class of compounds found in natural products,[18] but also an important synthetic motif in the synthesis of various heterocycles. (ii) The introduction of CF_3 is of great importance for the modification of this novel fragments. (iii) We have synthesized a new pyrrolidine bearing a spirocyclic skeleton motif *via* cascade cyclization.

On the basis of the above scenario, the commercially available azidotrimethylsilane ($TMSN_3$) was chosen as the nitrogen source to explore the reaction with 1,6-enyne **1a** and Togni's reagent **2a**.[19] Initially, the reaction was carried out in the present of 10 mol% $Cu(OAc)_2$ in DMF at 90 °C under argon. To our delight, the desired 2*H*-azirine product was isolated in 69% yield after 5 h (Table 1, entry 1). The molecular structure of **3a** was unambiguously confirmed by X-ray crystallography (see Supporting Information).[20] The study of various Cu pre-catalysts revealed that the Cu powder gave the best result (Table 1, entry 5). A brief survey on the solvent revealed that DMF is still the best choice for this reaction (Table 1, entries 5–9). An increased yield of the desired 2*H*-azirine (82%) was obtained when the reaction time was prolonged to 6 h (Table 1, entry 10). The reaction worked well under an air atmosphere and gave **3a** + **3a′** in 72% yield (Table 1, entry 11). Other attempts to promote this process proved to be less effective (see the Supporting Information). The control experiment suggested that the copper catalyst was essential to the transformation (Table 1, entry 12). In contrast, only a trace amount of 2*H*-azirine was observed with NaN_3 as nitrogen source (Table 1, entry 13). Finally, it was confirmed that the optimal reaction conditions were Cu powder (10 mol%) in DMF at 90 °C under argon for 6 h.[21]

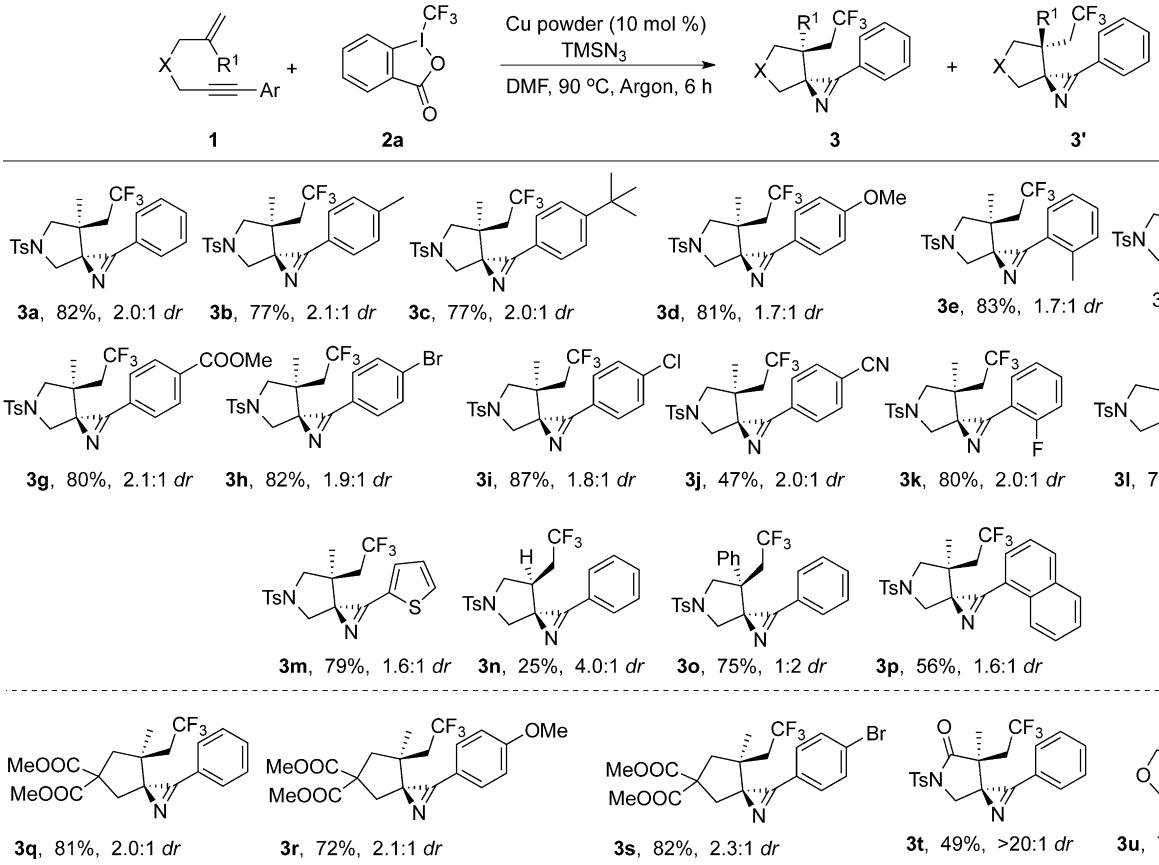
Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst	Solvent	*t* [h]	Yield [%][b]
1	$Cu(OAc)_2$	DMF	5.0	69
2	$CuSO_4$	DMF	5.0	trace
3	$Cu(OTf)_2$	DMF	5.0	62
4	$Cu(MeCN)_4PF_6$	DMF	5.0	70
5	Cu	DMF	5.0	76
6	Cu	CH_3CN	5.0	70
7	Cu	DCE	5.0	59
8	Cu	1,4-dioxane	5.0	56
9	Cu	NMP	5.0	35
10	Cu	DMF	6.0	82 (2.0:1 *dr*)
11[c]	Cu	DMF	6.0	72
12[d]	–	DMF	6.0	0
13[e]	Cu	DMF	6.0	trace

[a] *Reaction conditions:* **1a** (0.2 mmol), Togni's reagent **2a** (0.5 mmol), $TMSN_3$ (0.4 mmol), Cu powder (10 mol%), solvent (1.5 mL), 90 °C, under argon.
[b] Isolated yield (**3a** + **3a′**).
[c] Under air conditions.
[d] Without a copper catalyst.
[e] NaN_3 was used instead of $TMSN_3$.

Table 2. Scope of the copper-catalyzed cascade cyclization of 1,6-enynes.[a,b]

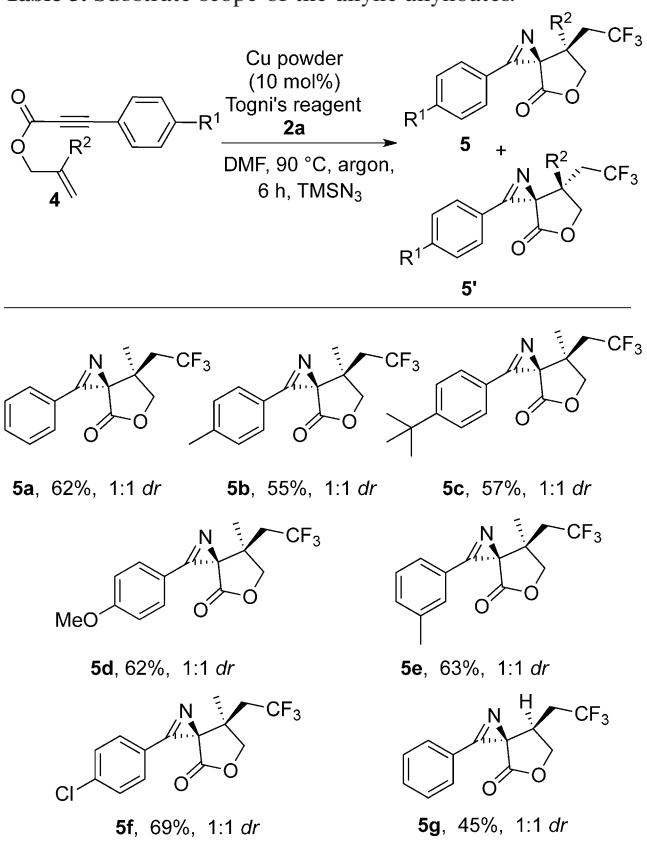


[a] *Reaction conditions:* **1** (0.2 mmol), Togni's reagent **2a** (0.5 mmol), $TMSN_3$ (0.4 mmol), Cu powder (10 mol%), DMF (1.5 mL), 90 °C, under argon, isolated yield.
[b] The ratio of diastereomers was determined by crude ^1H NMR. Structures of the major diastereomers are shown.

The optimal catalytic conditions were then applied to a range of 1,6-enynes to examine the substrate scope of this reaction. As summarized in Table 2, the reaction was not significantly affected by the substituents on the phenyl ring of the 1,6-enynes. Both electron-donating and electron-withdrawing groups performed well under the optimal reaction conditions (**3b–3l**). Meanwhile, this transformation was less affected by the substituent with a 2-thiophenyl group (**3m**) attached to the triple bond, which was obtained in 79% yield. It is worth noting that the unsubstituted allylic substrate (**1n**) afforded a decreased yield of 25% with a slightly improved diastereoselectivity (4.0:1 *d.r.*). This diastereomeric ratio is higher than those of all other substrates (except **3t**). This case suggests that the favored diastereomer may be a kinetic product and the other a thermodynamic product. As the yield increases, the thermodynamic diastereomer may be more prevalent, decreasing the diastereomeric ratio. In addition, enyne (**1o**) with a phenyl substituent efficiently participated in the reaction and provided the desired product **3o** in 75% yield with the diastereomeric ratio changed to 1:2. Substituents on the internal position of the alkene had a dramatic effect on the diastereoselectivities, and the selectivity towards product **3′** was increased with increased steric hindrance of substituents from H, Me to Ph (**3n**, **3a** and **3o**). The reaction also proceeded smoothly with a sterically-hindered naphthalene and gave the corresponding product **3p**. The reactivities of several carbon-tethered 1,6-enynes (**1q–1s**) were subsequently investigated, and the corresponding 2*H*-azirines (**3q–3s**) were obtained in good yields. The use of oxygen-tethered 1,6-enynes gave an excellent diastereoselectivity for spiro amide **3t** (>20:1 *dr*). Finally, the molecular structures of **3b′** and **3i′** were unambiguously confirmed through X-ray crystallography (see the Supporting Information)[20].

The butyrolactone skeleton is present in a wide variety of natural products with significant biological activities, such as antibiotic and anti-tumor properties.[22] It is also a versatile building block in organic synthesis. Encouraged by those versatile results and the unique role of butyrolactone, we wished to further investigate the scope of the reaction by using allylic alkynoates **4**. As shown in Table 3, allylic alkynoates

Table 3. Substrate scope of the allylic akynoates.[a,b]



[a] *Reaction conditions:* **1** (0.2 mmol), Togni's reagent **2a** (0.5 mmol), $TMSN_3$ (0.4 mmol), Cu powder (10 mol%), DMF (1.5 mL), 90 °C, under argon, isolated yield.

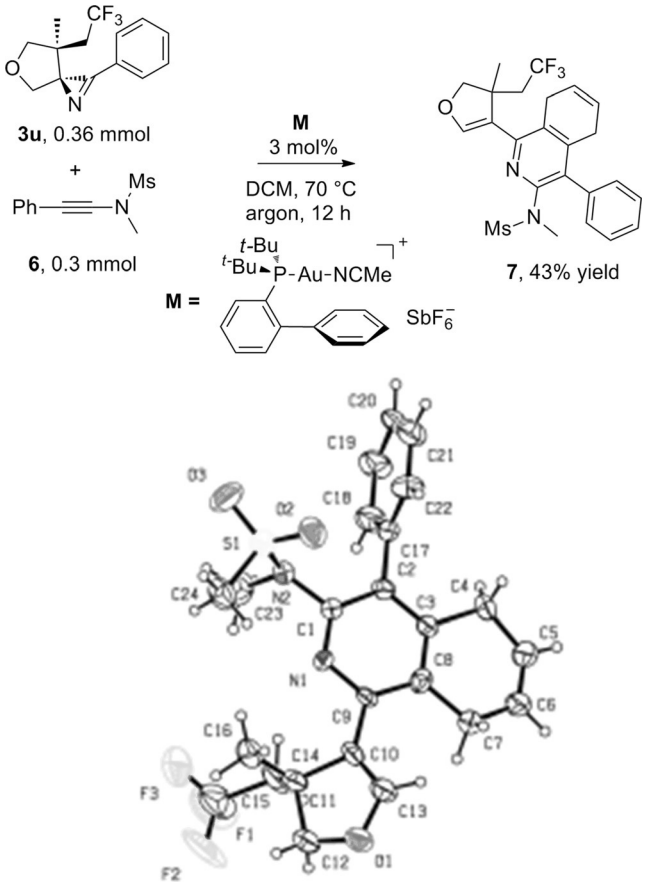
[b] The ratio of diastereomers was determined by crude ^1H NMR. Structures of the major diastereomers are shown.

4a–4g were smoothly transformed into the corresponding spiro-2*H*-azirines in moderate yields. The tolerance of the process for the halogen substituent in **4f** was remarkable, giving the desired product in 69% yield. These butyrolactone skeletons might prove to have some potential value in medicinal chemistry in the future.

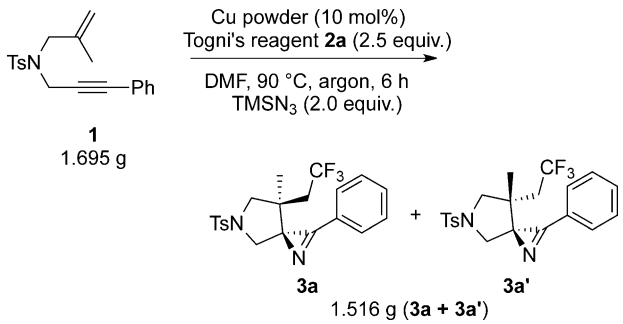
This copper-catalyzed synthesis of spiro-2*H*-azirines proved to be synthetically useful to construct complex heterocycles in organic chemistry. For instance, spiro azirine product **3u** was reacted with ynamide **6** in the presence of 3 mol% of gold complex **M** in DCM at 70 °C for 12 h,[23] the cycloaddition occurred smoothly and gave the spiro product **7**[20] in 43% yield (Scheme 2).

Furthermore, the reaction could be easily scaled up to 1.7 gram and gave the desired product in a good yield (Scheme 3).

The possible mechanism for the transformation of 1,6-enynes into 2*H*-azirines was also studied (Scheme 4). The reaction without $TMSN_3$ was carried

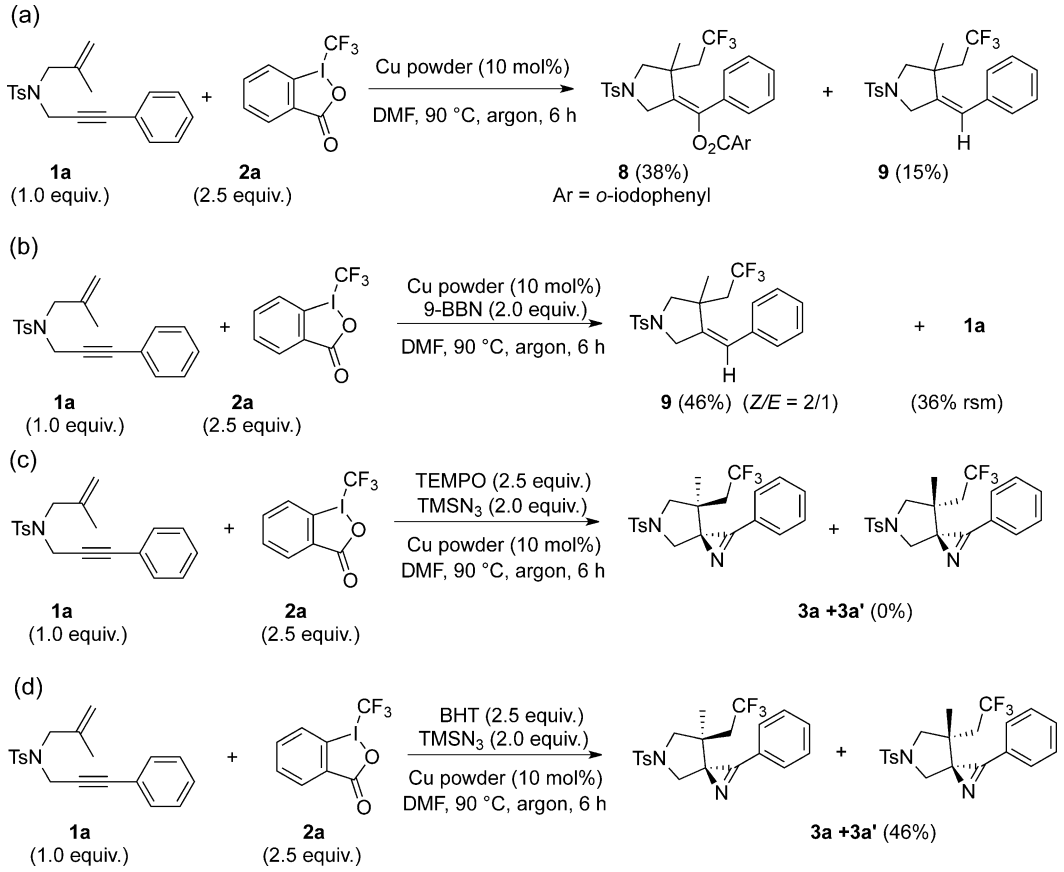


Scheme 2. Further synthetic transformations.

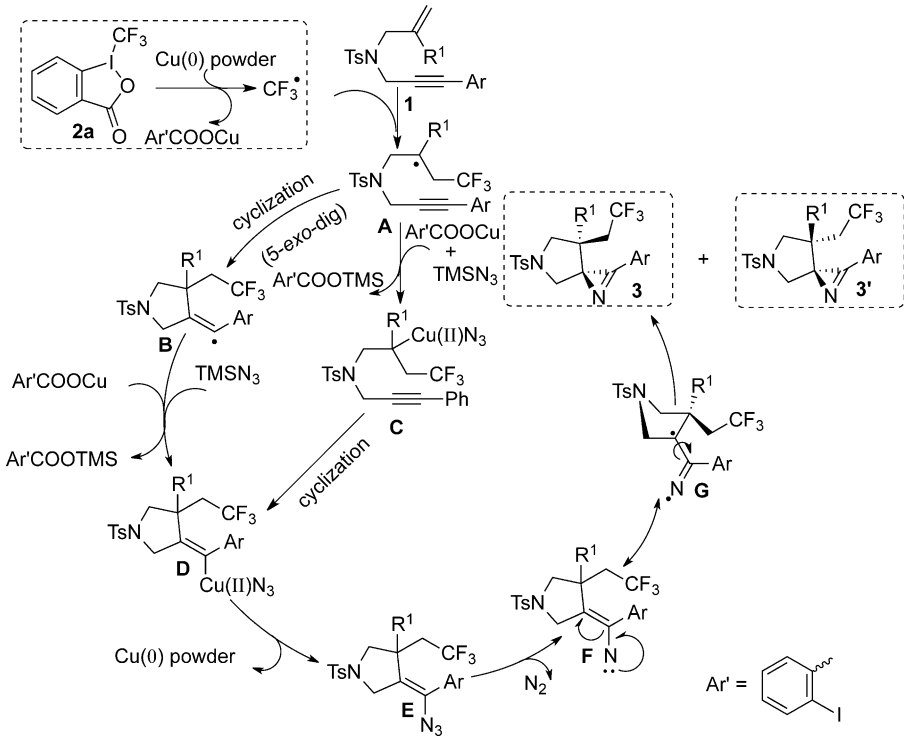


Scheme 3. Gram-scale reaction.

out to detect the corresponding CF_3 addition products. Both oxytrifluoromethylation product **8** (38%)[24] and hydrotrifluoromethylation product **9** (15%) were obtained under the optimized conditions (Scheme 4a). An increased yield of hydrotrifluoromethylation product (46%) was observed when 2.0 equiv. of 9-borabicyclo[3.3.1]nonane (9-BBN) were added as hydride source (Scheme 4b). Moreover, when the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added to the reaction system, no product was detected with 89% of the starting material being recovered. With another radical inhibitor 2,6-di-*tert*-butyl-



Scheme 4. Trapping experiments.



Scheme 5. Proposed mechanism.

4-methylphenol (BHT), a decreased yield (46%) of the desired product was observed. On the basis of the above results, literature precedents,[25,26] and our previously research results,[27] we propose the following mechanism (Scheme 5). Firstly, Togni's reagent **2a** is reduced by Cu powder to afford a CF_3 radical, which reacts with 1,6-enyne to generate the radical intermediate **A**. After cyclization by a 5-*exo*-dig process, the vinyl radical intermediate **B** is formed. Secondly, the vinyl radical intermediate **B** reacts with (2-iodobenzoyloxy)-copper(II) and $TMSN_3$ to generate the copper(II) azide complex **D**, which could also be obtained from the cyclization of intermediate **C**. Subsequent reductive elimination of intermediate **D** gives the azide **E**. The release of nitrogen from azide **E** generates alkenyl nitrene **F**, which is considered as a valuable synthetic equivalent of 2*H*-azirine. Finally, the spiroketal products as pairs of diastereomers were obtained followed by intermediate **G**, which is just a resonance structure of the alkenyl nitrene **F**.

In summary, we have developed an efficient copper-catalyzed cascade cyclization of 1,6-enynes for the synthesis of spirocyclic skeleton 2*H*-azirines. Compared to the traditional synthesis methodology, our the developed reaction systems could introduce an important pharmaceutically active group (CF_3) simultaneously, and provide a facile access to various spirocyclic skeleton motifs. Further exploration on the basis of this strategy, especially the biological activity of spirocyclic lactones, is currently underway in our laboratory.

Experimental Section

General Procedure

An oven-dried tube was charged with 1,6-enyne (0.2 mmol), Togni's reagent **2a** (0.5 mmol) and Cu powder (0.02 mmol). The tube was evacuated and backfilled with argon. Then, $TMSN_3$ (0.4 mmol) dissolved in DMF (1.5 mL) was added. The reaction mixture was stirring at 90 °C for 6 h and hen extracted with DCM. The combined organic layers were washed with saturated brine, dried over Na_2SO_4, concentrated under vacuum and purified by flash column chromatography to afford the product.

Acknowledgements

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[20] CCDC 1035654, CCDC 1035653, CCDC 1035652, and CCDC 1401823 (compounds **3a**, **3b′**, **3i′**, and **7**, respectively) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[21] See the Supporting Information for detailed data.

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